SEMI-ANNUAL TECHNICAL REPORT Period ending 7-14-68

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Title: "Neurohumoral Control Systems Operation In Adjustment of Ventricular Performance"

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SEMI-ANNUAL TECHNICAL REPORT

SUMMARY STATEMENT OF PROGRESS

SPECIFIC AIMS:

I. To develop and study the behavior of an externally operated control system for the "On-Line" adjustment of head pressure in instrumented, awake animals (with activated aortic arch mechanoreceptors) that simulates, and yet is capable of preventing, the usual moment to moment changes in cardiac and peripheral vascular adjustments that result from carotid sinus mechanoreceptor reflex activity for long periods of time.

II. To determine, define, and evaluate the extent and relative significance of carotid sinus mechanoreceptor reflex activity in the moment to moment and long term modulation of ventricular performance.

In seeking to achieve these objectives it was considered a necessity first to define the operation of the mechanoreceptor reflexes in terms of their behavioral characteristics in adjusting cardiac performance from moment to moment in intact awake animals. In short, an effort must first be made to describe as precisely as possible the operation of the carotid sinus and the aortic mechanoreceptor reflex mechanism. For this a mathematical model is desirable. It is assumed that the study of this model by use of computer simulation techniques will be an informative and necessary prerequisite to the achievement of the first specific aim stated above.

In deriving a mathematical expression to describe the operation of these reflexes, and their effectiveness and manner of controlling heart rate, stroke volume, peripheral resistance, and arterial pressure, at least two general procedures must be undertaken. First, recordings must be made of the changes in the appropriate variables indicative of behavior of the system in response to specific forcing functions. In formulating an hypothesis to describe this system, a block diagram must be drawn to represent all physical and chemical processes thought to compose the system. In doing this, all the available information, derived from studies by others, as well as directly obtained data from experimental animal studies, should be used in order that the final model which describes the kinetic properties of the system might account for all properties known to be present in such a system.

Our first observation has been that although innumerable studies have been made of the operation of the carotid sinus and aortic depressor reflexes in the control of heart rate, stroke volume, myocardial contractility, and arterial pressure, most of these studies have not been carried out in the intact unanesthetized animal. Further, the studies of Rushmer

(Amer. J. Physiol. 205: 1000, 1963) and others suggest that these reflex mechanisms may operate quite differently in the "uncontrolled" environment of the intact animal. In view of this lack of information, we have been investigating during the past six months the effects of carotid sinus hypotension on cardiac function and aortic pressure in awake, intact dogs.

Dogs were instrumented for study in the awake state using cuffs as seen in Figure 1. Measurements were made of the simultaneous changes occurring in brachiocephalic artery pressure (above the point of cuff constriction), aortic pressure, ventricular pressure and left ventricular external circumference changes. The left subclavian was ligated so that all head pressure and blood flow was via the brachiocephalic artery.

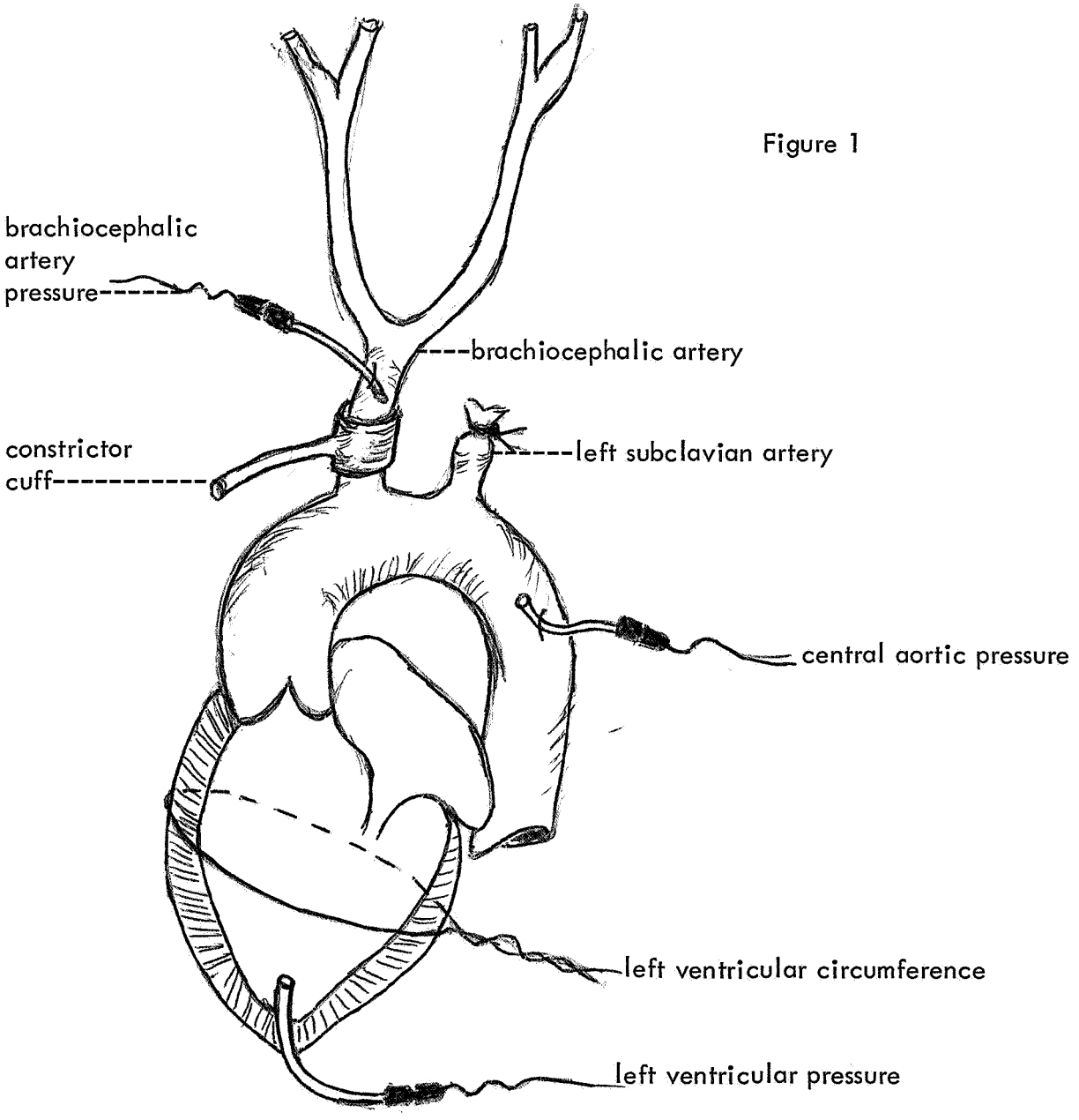

Figure 1

To date, a total of ten dogs have been studied. Figure 2 shows the typical response in terms of heart rate and pressure change occurring during periods of temporary brachiocephalic artery occlusion.

First, it is seen that the arterial pressure in the head region drops to approximately 60 mmHg during the period of occlusion (left subclavian artery is ligated in all these animals).

No change in either heart rate or Dp/dt occurs in spite of a clear rise in heart size (left ventricular circumference, LVC), increase in peak systolic left ventricular pressure and an increase in central aortic pressure.

These results show that there is no necessary relation between the reflex cardiac effects and peripheral vascular response to carotid hypotension in the unanesthetized closed chest dog. These results are contrary to those that are usually quoted in the literature for indeed one would have expected to see an increase in heart rate and Dp/dt occurring in these dogs during the period of carotid sinus hypotension.

In Figure 3 is shown the response observed in awake dogs several days post operative. Typically at this time the ambient heart rate is slow (approximately 60/minute) and the dogs exhibit sinus arrhythmia. Temporary carotid sinus hypotension (induced by inflation of the cuff around the brachiocephalic artery) causes both an increase in heart rate and a rise in central aortic pressure. This is associated with a rise in left ventricular end-diastolic pressure, no significant change in Dp/dt and an increase in heart size (both at end diastole and end systole).

Figure 4 is shown to indicate the different type of response seen to carotid hypotension in dogs with which the aortic nerves have been sectioned or the ascending and aortic arch have been "skeletonized" (debuffered). The recording was taken from a dog eight days after surgery for instrumentation. Typically the ambient heart rate in these animals is higher and sinus arrhythmia is absent. Carotid sinus hypotension routinely causes an increase in Dp/dt and heart rate as well as central aortic pressure. In spite of this, however, left ventricular end diastolic pressure rises.

In intact, awake dogs, elevation of aortic and carotid sinus pressure with drugs whose major effect is to increase peripheral resistance (phenylephrine) cause a sustained elevation in arterial pressure along with significant bradycardia with the heart rate frequently dropping to 40 beats per minute. Dp/dt is decreased and when carotid sinus hypotension is induced during this response a further rise in aortic pressure occurs, heart rate increases, peak Dp/dt increases, and left ventricular end-diastolic pressure rises further, and the heart enlarges more at end systole and end diastole.

A surprising result, however, was obtained when these interventions were induced in dogs after blockade of the beta adrenergic receptors with propanolol. In Figure 5 is shown a typical example of such an experiment. The dog was studied in the awake state ten days after surgery for instrumentation. Prior to the record shown this dog had received propanolol (2 milligrams/kilo) and the existence of beta adrenergic blockage was established. This later was shown to be present by the lack of response to an injection of isoproterenol in a dosage which prior to propoanolol administration had caused a profound increase in heart rate, and peak Dp/dt and

a fall in central aortic pressure.

The recording shown in figure 5 is from the same dog and was taken on the same afternoon as that shown in Figure 3. The recordings are made at the same paper speed (1mm/sec). By looking back at Figure 3 it can be seen that the ambient heart rate of this animal was 60 beats/minute and that sinus arrhythmia was present before propanolol administration. In Figure 5 the recording was taken after beta blockage had been established. The ambient heart rate during the control period was 72/minute and sinus arrhythmia had disappeared. At the arrow marked (1) a single injection of phenylephrine, 100 micrograms/kilo, was made rapidly. Aortic pressure rose to 180 mmHg and heart rate fell to 30/minute. Now, with induction of carotid sinus hypotension at (2) by constriction of the brachiocephalic artery cuff, the heart rate increased to 72/minute initially and finally to 86/minute. There was no increase in peak Dp/dt above control. Left ventricular end diastolic and systolic size, as well as end diastolic pressure are increased throughout the intervention. This increase in heart rate could not have been due to an increase in cardiac sympathetic nerve activity, and therefore is a result of a withdrawal of vagal tone from the heart.

SUMMARY

In general these kinds of experiments have not been performed in awake animals by other investigators. Therefore information of this kind is not available from the literature. It appears that the ability to lower head pressure in a direction opposite to that of a central aortic pressure change through use of a cuff about the brachiocephalic artery is a very helpful maneuver. It is to be emphasized that in all these studies the left subclavian artery was ligated, thus all blood supply to the head of these animals passes through the brachiocephalic artery.

The main points discovered in these preliminary experiments may be summarized as follows:

1. A significant fall (to as low as 40 mmHg) in head pressure and therefore carotid sinus pressure bilaterally can be easily produced by temporarily occluding a cuff placed about the brachiocephalic artery in awake instrumented dogs that have left subclavian artery ligation.

2. The special cuffs used are rugged yet light weight structures which communicate to the exterior through thick walled silastic tubes. The cuff pressure and volume can be quickly adjusted to any desired level and held, thus making them highly suitable for servo control.

3. Carotid sinus hypotension induced in awake dogs well past their recuperative period following surgery for instrumentation, can be carried out without pain or discomfort to the animal.

4. Sudden and temporary carotid sinus hypotension in awake dogs typically increases heart rate, aortic pressure, left ventricular end-diastolic pressure and heart size, both end-diastolic and end-systolic. Little of no change is seen however in the level of peak Dp/dt. Since Dp/dt did not increase even though the left ventricular diastolic pressure was elevated we can conclude that this "index of myocardial contractility" suggests there was no positive inotropic effect from the interventions, for a positive inotropic by this yardstick would have required a finding of no

change in left ventricular end diastolic pressure and an increase in peak Dp/dt. This analysis is based on the studies of Mitchell and associates (Amer. J. Physiol. 205: 41-48, 1963).

5. In awake dogs with complete "beta adrenergic receptor blockade" after propanolol infusion (as evidenced by lack of a heart rate or pressure change to intravenous injection of a high dose of isoproterenol (12 micrograms) temporary carotid sinus hypotension caused a reversal of the bradycardia induced by phenylephrine infusion. In addition, central aortic pressure was elevated above the pressure level present as a result of the pressor response to the infusion (Figure 5).

6. Carotid sinus hypotension can increase heart rate significantly by either inhibiting cardiac vagal activity or by increasing sympathetic activity, or both.

The concept expressed in #6 is contrary to the current view recently advanced by Glick and Covell (Amer. J. Physiol. 214: 955-961, 1968) and Glick and Braunwald (Circ. Res. 16: 363, 1965). Glick and Covell, for example, stated in their article "Our findings indicate that, under the condition employed, the aortic arch and carotid sinus baroreceptors play a similar role in the reflex regulation of heart rate. However, in some of the studies the aortic arch receptors appeared to predominate but in no instance did the carotid sinus receptors seem more important, although their synergistic activity could be demonstrated". They further comment, "The findings reported here also strongly suggest that a positive input produced by raising pressure is a more powerful stimulus than a negative input of lowering perfusion pressure. Thus when perfusion pressure was altered in an opposite direction in the two baroreceptor areas, heart rate always slowed, irrespective of whether the positive input was into the aortic arch or into the carotid sinus region".

This clearly was not the case in our studies as evidenced by Figure 5. Perhaps the greatest reason for the difference in our findings and theirs is embodied in their statement, "Our findings indicate that under the conditions employed...". They studied anesthetized open chest dogs, we are studying intact, awake animals.

Earlier Glick and Braunwald (Circ. Res. 16: 363, 1965), in discussing the relative roles of the sympathetic and parasympathetic nervous systems in the reflex control of heart rate, stated, "Our results indicate that cardiac slowing produced by acute elevations in pressure apparently stems from parasympathetic stimulation, withdrawal of sympathetic activity having no significant effect". They continued, "On the other hand, the cardiac acceleration produced by acutely reducing arterial pressure results from the activity of the sympathetic nervous system, withdrawal of parasympathetic activity playing no detectable role".

On the basis of these observations they came to the conclusion that "These findings are not consonant with the traditional concept of control of heart rate which predicates simultaneous reciprocal changes in activity occurring in the two components of the autonomic nervous system".

Our own preliminary investigations as presented above once again illustrate the difficulty of interpretation and application of experimental data, by necessity obtained under a set of certain special conditions, to the intact functioning organism. At present, there are divergent conclusions arrived at by different investigators as to the role of various factors in cardiac regulation.

In the second stage of our investigation we plan to control the level of head pressure accurately through use of a servo control system. This will allow for precise adjustment of the brachiocephalic artery cuff pressure.

Figure 1a. Special cuffs used, a large cuff for aorta constrictions, small cuff for brachiocephalic artery.

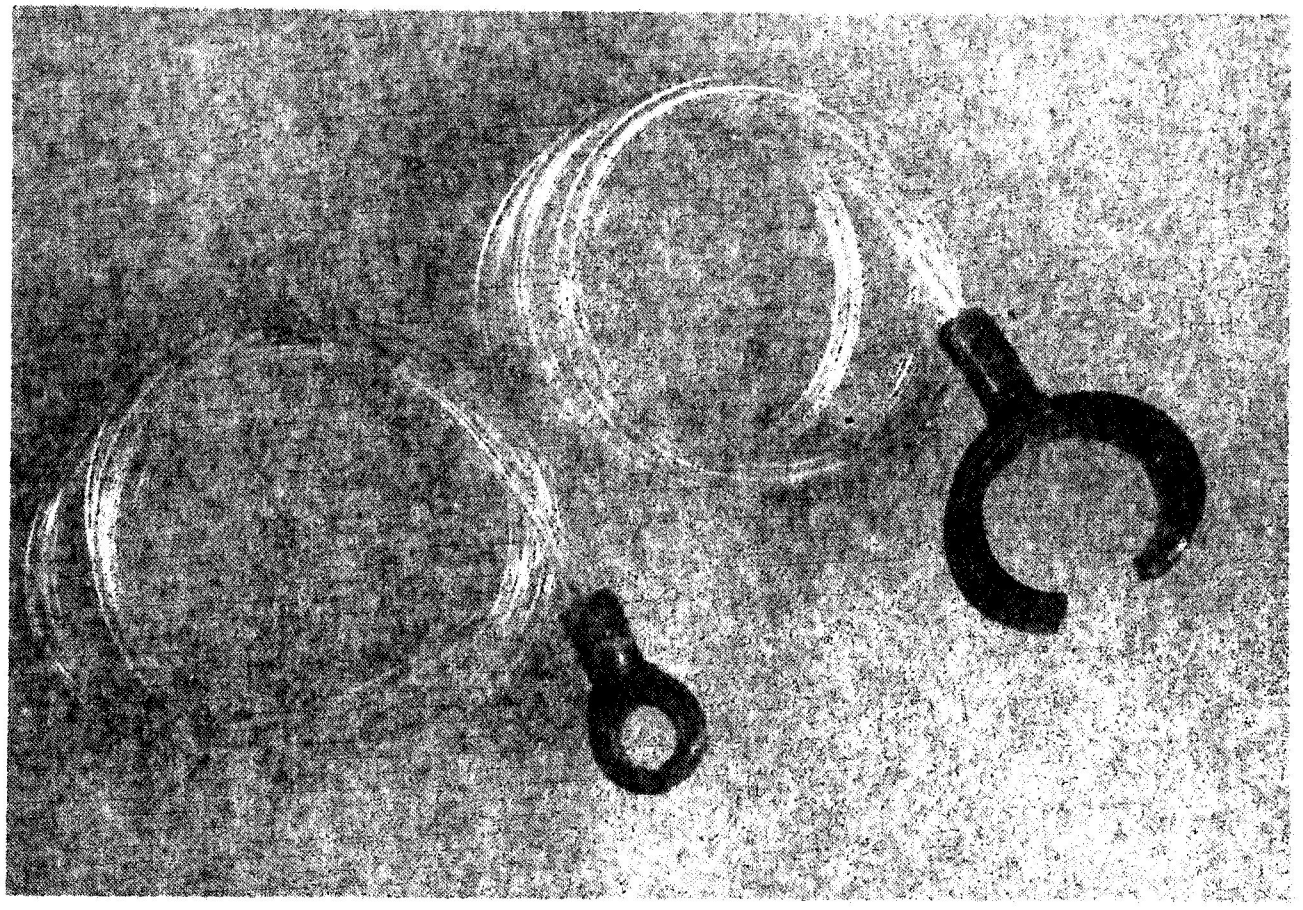

Figure 2. Heart rate and pressor response to carotid sinus hypotension in anesthetized dog.

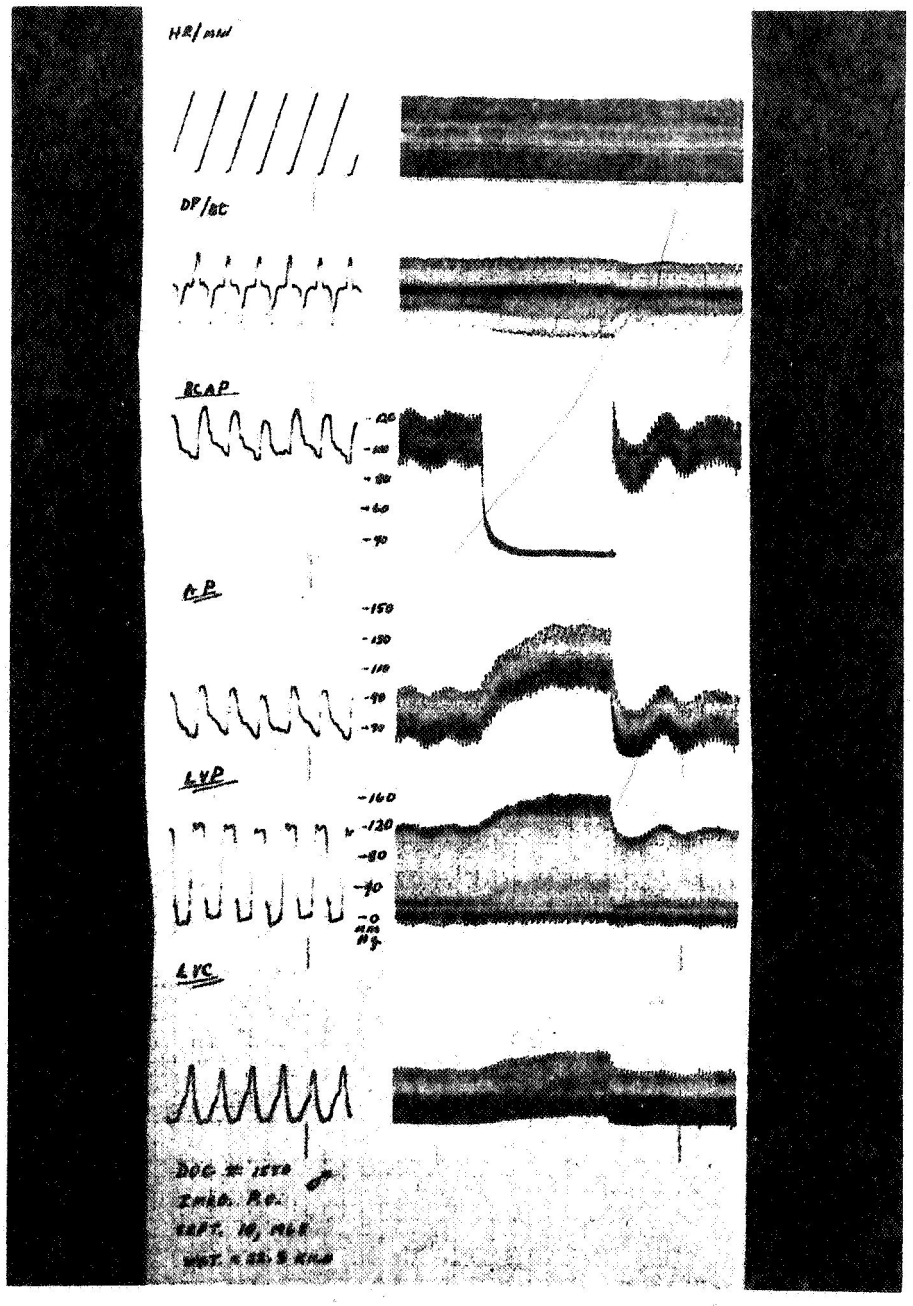

Figure 3. Heart rate and pressor response to carotid sinus hypotension in an awake dog 10 days after surgery.

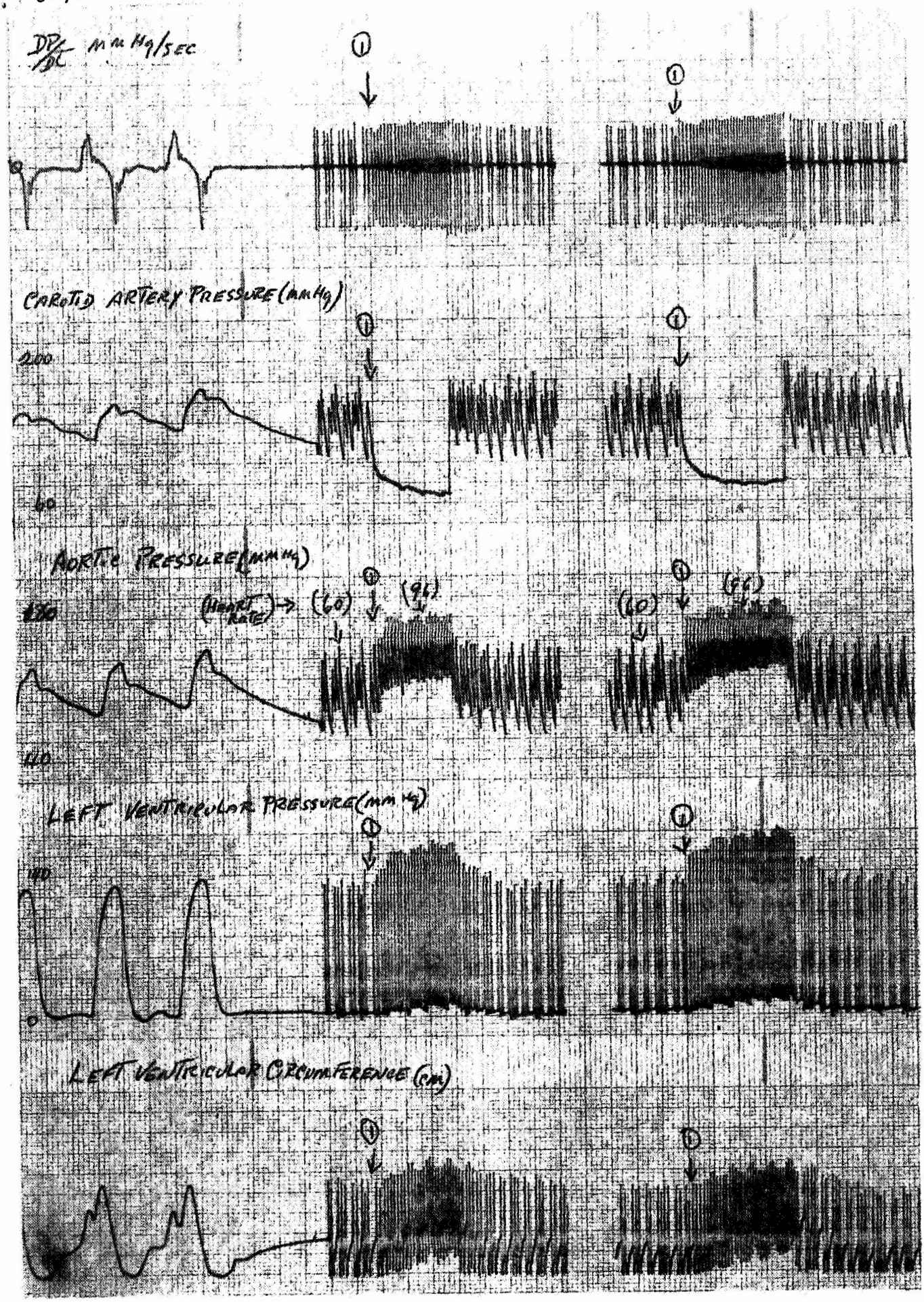

Figure 4. Heart rate and pressor response to carotid sinus hypotension in an awake dog 8 days post operative with aorta debuffered.

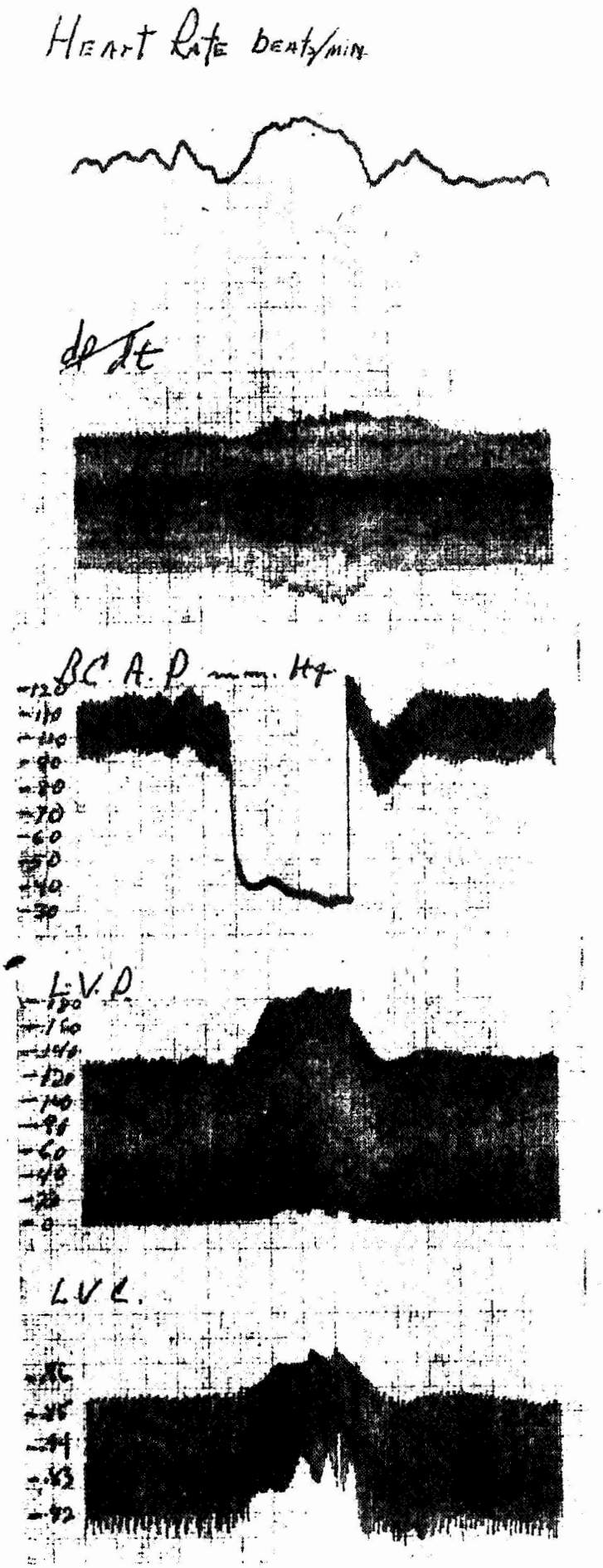

Figure 5. Heart rate response to carotid sinus hypotension superimposed on the pressor and bradycardiac response to injection of phenylephrine (awake dog 10 days post operation). (dog has "beta receptor blockade")